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Insomnia Caused by Medical Disorders

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Abstract

Virtually any medical condition can cause sleep disruption. The incidence of insomnia increases with age as medical problems increasingly occur, and patients with chronic insomnia are more likely to develop adverse health outcomes due to medical disease. There are multiple ways in which insomnia may be caused or aggravated by medical illness or bodily injury. Unpleasant stimuli can directly impede initiation of sleep, or they may cause frequent arousals or awakenings. Changes in basic systemic physiology (such as disorders of ventilation) may produce similar disruption in sleep continuity. There may be humoral changes that have direct neurochemical or neurophysiological effects, augmenting vigilance and lowering the threshold to arousal from sleep. The effects of acute and subacute sleep disruption can lead to chronic psychophysiological insomnia by creating the anticipation of disturbed sleep and by altering circadian entrainment, further accentuating the disruptive effects of the underlying medical condition. Difficulties with insomnia may persist long after the causative medical condition has been effectively managed.

Keywords: Eczema, End-stage renal disease, Gastroesophageal reflux disease, Congestive heart failure, Asthma, Allergies, Hyperthyroidism, Arthritis

Introduction

Virtually any medical condition can cause sleep disruption. The incidence of insomnia increases with age as medical problems increasingly occur [1], and patients with chronic insomnia are more likely to develop adverse health outcomes due to medical disease [2]. There are multiple ways in which insomnia may be caused or aggravated by medical illness or bodily injury. Unpleasant stimuli can directly impede initiation of sleep, or they may cause frequent arousals or awakenings. Changes in basic systemic physiology (such as disorders of ventilation) may produce similar disruption in sleep continuity. There may be humoral changes that have direct neurochemical or neurophysiological

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effects, augmenting vigilance and lowering the threshold to arousal from sleep. The effects of acute and subacute sleep disruption can lead to chronic psychophysiological insomnia by creating the anticipation of disturbed sleep and by altering circadian entrainment, further accentuating the disruptive effects of the underlying medical condition. Difficulties with insomnia may persist long after the causative medical condition has been effectively managed.

When describing the medical causes of insomnia, the most frequently recurring theme is the disruptive influence of painful or unpleasant stimuli on sleep initiation and maintenance. The polysomnographic appearance of sleep disturbance caused by medical conditions is nonspecific, and most times is no different than any other form of insomnia [3, 4]. The diagnosis is most often made by clinical correlation, requiring a thorough review of a patient's general medical profile and a complete physical examination. After a polysomnogram has been recorded to evaluate for any detectable cause of sleep disruption, an empirical approach to treatment can begin.

Treatment of secondary insomnia draws upon all of the commonly utilized behavioral, pharmacological, and alternative medical approaches utilized in primary insomnia [5, 6]. Optimizing the treatment of the underlying medical condition is the cornerstone of effective insomnia management, along with attempts to improve the quality of sleep. Ultimately, the treatment must also take into consideration potential complications produced by the medical condition(s), either a change in the natural course of the disease, or an untoward response to well-intended pharmacological insomnia therapy. In cases where the medical condition has an intermittent character, short-term or intermittent pharmacotherapy for insomnia may be the best approach. In progressive medical disorders, the management of associated insomnia may require elaboration over time, with an evolving pharmacotherapeutic approach. More complicated cases should compel frequent review of the applied management strategies, in order to avoid the maintenance of suboptimal therapy, the continuation of pernicious medications, and the ultimate surrender of the patient to decline in level of function as sleep disruption becomes more profound.

An attempt to comprehensively review major medical disorders is bound to leave some conditions unaddressed. For most conditions there is only anecdotal information or brief mention of insomnia as a feature of the disease process. Perhaps the best way to frame the discussion is an approach to each organ system, allowing for the collection of related disorders that may share a common overall effect on sleep continuity. This parallels the method used by physicians to categorize the symptomatic profile (the Review of Systems) for a given patient, allowing for an orderly review of potential medical issues during a general medical examination. The unique role of each organ system in sleep disruption can be reviewed, even for disorders of completely disparate etiology (for example, a neoplastic versus inflammatory cause of disease), along with the shared treatment issues.

Skin Conditions and Insomnia

The skin is the body's largest organ, serving to sequester and protect the internal environment from the outside world, and providing some of the most profound early alerts of important environmental issues. It has the densest collection of nerve terminals outside of the central nervous system. Any condition that imposes damage, pressure, or irritation on the dermis will cause pain

through dermal nerve endings, and the pain will disturb the integrity of sleep. Infectious, allergic, or inflammatory skin conditions are common potential causes of disturbed sleep initiation and maintenance.

A recent pilot study reported that 93.75% of adults surveyed with active dermatological issue had insomnia [7].

Pain due to minor or major burns frequently delay sleep initiation, and may become aggravated by involuntary body shifting during sleep. The acute phase of burn healing may be incredibly painful and last several months in severe cases, and this is the time of greatest sleep disturbance. The healing process may leave scar tissue that is unusually sensitive or restrictive, prolonging the negative influence on sleep quality. In a cohort suffering from herpes zoster reactivation, insomnia was one of the most bothersome symptoms reported (25%), second only to pain [8]. Lacerations have a shorter time of healing, but may produce nerve injury, and the subsequent reinnervation can cause paroxysms of sharp pain, burning pain, or dull aching pain. Swelling of soft tissues due to edema may be transient, intermittent, or chronic, but causes epidermal discomfort that delays sleep onset and impairs sleep maintenance. Pathological diaphoresis may be sufficiently severe to cause awakening due to cold, damp bedclothes or sheets [9]. The use of occlusive dressings, bandages, or splints may produce discomfort and restrict movement during sleep. Oral corticosteroid medications may produce insomnia [10], particularly at higher doses, especially during the initial period of use.

Atopic dermatitis is a known cause of insomnia especially among children. Pruritus and scratching are the main causes of sleep disturbances in this condition [11].

A recent study showed that watching comedic films prior to going to sleep reduced the amount of awakenings at night in patients with atopic dermatitis as compared to watching nonhumorous films [12].

Interestingly, insomnia appears to be the most important psychosomatic symptom that is a predisposing factor for chronic urticaria, a condition characterized by skin weals and pruritus, which can itself disrupt sleep thus creating a vicious cycle [6].

Amelioration of a skin condition may require a relatively short duration of treatment, causing only short-term sleep disruption. The use of hypnotic medication, especially shorter-acting medications that are unlikely to produce daytime sedation, may be ideally suited to a skin condition that has brief course (such as poison ivy dermatitis) or intermittent exacerbation (such as eczema). Many of the antihistamine medications used to reduce allergic response and reduce itching are sedating, improving sleep initiation and maintenance somewhat, but there may be residual daytime effects on alertness and cognitive performance [13]. The use of medications such as amitriptyline or trazodone, which may improve the component of insomnia caused by depression and pain, should be considered if the duration and severity of insomnia warrants their use, and if other medical conditions do not preclude their use.

Upper Airway Problems and Insomnia

Problems in the nasopharynx, oropharynx, and larynx are a common cause of sleep disruption. The most widely recognized condition that can be caused by the pharyngeal tree is obstructive sleep apnea (OSA). Mass lesions, hyoid

pathology, and cervical spine degenerative changes [14] can also cause obstructive apnea. For a detailed discussion of insomnia due to OSA the reader is referred to Chap. 19 of this book.

Postnasal drip caused by chronic allergic rhinitis or chronic/recurrent sinusitis may cause frequent awakening by stimulating cough during sleep [15]. Severe allergic rhinitis impairs all dimensions of sleep, causing severe insomnia and reduced quality of life regardless of whether the rhinitis is intermittent or chronic [16]. Allergic, infectious, or inflammatory pharyngitis can impair sleep continuity through the occurrence of local pain, which may be worsened upon swallowing, or may stimulate frequent reflexive swallowing. Sleep-related laryngospasm or choking is a rare sleep disorder first described by Chodosh in 1977 [17]. Its symptoms include periodic and sudden awakenings with the feeling of choking and a brief period of stridor that progresses to normal breathing [18]. It may cause sufficient distress that the security of sleep is threatened [18]. Most common contributor to nocturnal laryngospasm is gastroesophageal reflux disease [19] but other factors include postnasal drip, otolaryngological tumors, metabolic factors such as hypoparathyroidism [20], multisystem atrophy (MSA) [21], iatrogenic factors such as postextubation [22], and psychological disturbances [19]. These conditions lead to the irritation of the superior laryngeal nerve hence causing the spasm [19]. Prevention and treatment in most cases is focused on treating the underlying cause. In rare cases (with MSA) CPAP [23] and acupuncture [22] have been helpful

Any painful condition affecting the airway can negatively affect the quality of sleep, and when present for a sufficient duration or with sufficient frequency, can cause insomnia [24]. Assessment of the head and neck may not provide sufficient evidence of pathology in some cases. The diagnostic clue on a routine PSG would be frequent bursts of submental myogenic activity, which in isolation could also be interpreted as bruxism or a reflection of a nocturnal periodic movement disorder. In this case, the bed partner's observations or the use of good quality video/audio during PSG may help to identify the cause of sleep disruption, and help to appropriately direct treatment.

Pulmonary Disorders and Insomnia

Pulmonary disorders frequently cause some degree of sleep disruption, which can develop over time into secondary insomnia. Nocturnal Asthma causes poor efficiency sleep and secondary impairment of cognitive function even when the asthma symptoms are fairly stable; more frequent attacks of bronchospasm at night would worsen insomnia as well [25, 26]. Since nocturnal asthma attacks can be fatal, aggressive treatment is warranted which in of itself can lead to insomnia. Medications used to treat asthma, including bronchodilators such as albuterol, the methylxanthines derivatives theophylline and caffeine, and even inhaled steroid medications have an activating effect on the central nervous system, which may prolonged sleep initiation and increase the likelihood of arousal from sleep. Some suggest using theophylline in the early evening or steroids in the afternoon improve both nocturnal lung function and sleep as opposed to conventional schedules [27, 28]. Chronic obstructive pulmonary disease (COPD) [29] can also lead to significant insomnia. For a detailed discussion of COPD and insomnia the reader is referred to Chap. 19. Other pulmonary conditions such as restrictive changes in the pulmonary bed [30],

bronchitis, pneumonitis, pleuritis, and neoplasia of the pulmonary tree can cause disruption of ventilation, waxing/waning hypoxia [31], cystic fibrosis [32], chest wall pain, and cough that lead to frequent arousal and poor sleep continuity. Chronic hypoxia and hypercarbia gradually desensitize carotid and CNS medullary chemoreceptors, causing central apnea that can worsen the magnitude of ventilatory pathology, and thereby the chronic nature of sleep disruption. The appearance of sleep-disordered breathing in association with pulmonary disease is well-appreciated by the medical community, but optimal sleep quality may not immediately return despite effective management of the pulmonary problem. The medications used in the treatment of secondary insomnia due to pulmonary dysfunction must be chosen carefully. The level of oxygenation and the persistence of ventilatory drive may be challenged by even the short-acting hypnotic medications, and hypnotics with more muscle-relaxing qualities may compromise the additional ventilatory effort offered by chest wall musculature. The use of tricyclic antidepressant medications is relatively contraindicated in asthma, due to their propensity to aggravate bronchiolar constriction. Nonpharmacological treatments (sleep restriction, light therapy) may be paired with very low doses of short-acting hypnotic medications to enhance sleep initiation and continuity, and the serotonin reuptake inhibitor paroxetine may have slightly sedating and anxiolytic properties that prove useful for the treatment of secondary insomnia due to pulmonary disease. Although nocturnal supplemental O_2 is the mainstay of treatment for COPD-related insomnia [31], its role in restrictive lung diseases has not studied. Careful bronchial hygiene is an important adjunct therapy modality in all cases.

Cardiovascular Diseases and Insomnia

Cardiovascular diseases cause sleep disruption through nocturnal angina [33, 34] abnormal sensations such as palpitations or tachycardia [35], paroxysmal dyspnea, or orthopnea related to congestive heart failure. More severe congestive heart failure produces ventilatory changes during sleep as well, with periodic breathing of Cheyne-Stokes character, or central apnea that produces frequent arousals from sleep [36]. Orthopnea may require that a patient is only able to recline slightly while sleeping, and the resulting disturbance of sleep continuity may be significant. Acute insomnia is a common sequela of myocardial infarction [33]. The medications used to treat cardiac disturbance may aggravate sleep disruption. Vasodilating agents may produce headache that disrupts sleep continuity, as may the rebound effects of morphine when it is used intermittently. Digoxin may produce side effects including insomnia and headache, especially at higher blood levels. Diuretic therapy at night causes frequent awakening to urinate. The symptoms of cardiac disease and potentially pernicious effects of its treatment are usually superimposed on the typical sleep fragmentation of elderly individuals, but the chronicity and severity of cardiac disturbance will largely determine whether secondary insomnia becomes sufficiently severe to require treatment. Once medical therapy has been optimized, the ideal approach will select therapy that has the least chance of casing medical complications. As with severe pulmonary disease, longer-acting hypnotic medications are more likely to cause ventilatory compromise. Tricyclic antidepressant medications can increase the possibility of cardiac arrhythmia, and are relatively contraindicated. Trazodone may be somewhat

less likely to cause arrhythmia, but like the tricyclic agents, its residual effects in the daytime may cause fatigue or hypersomnia. Creative treatment with shorter-acting hypnotic medications may be combined with efforts to maximize physical comfort through special furniture, such as a hospital bed, to promote blocks of restful sleep lasting a few hours at a time. Monophasic sleep may need to be sacrificed, in favor of two or three smaller blocks of sleep that take advantage of the natural periods of drowsiness that occur during the day. Treatment of disturbed ventilation may help sleep continuity, avoid hypoxia, and provide more refreshing sleep, but CPAP therapy is not well-tolerated, and can actually aggravate central apnea. Biphasic positive pressure ventilation may avoid exacerbation of central apnea, and may be more tolerable in its promotion of normal ventilatory tidal movement.

Digestive Disorders and Insomnia

Disorders of the gastrointestinal system may produce significant sleep disturbance leading to secondary insomnia [37]. The primary problem may remain occult, and if a sleep study shows only the typical features of insomnia, the benefit of insomnia management may be limited over the course of months or years. GERD worsens with reclining, especially if a person has eaten within an hour or two of sleep, and up to two-thirds of people with GERD have nocturnal symptoms that disturb their sleep [38]. GERD is also worsened by obstructive breathing, as the increase in intrathoracic pressure produces an increase in abdominal displacement, causing more pressure within the GI lumen and more tendency for reflux through a hypotonic or incontinent lower esophageal sphincter. The irritation of the esophageal mucosa causes arousal from sleep, which appears on PSG to be spontaneous, without correlation on ventilatory or EMG channels. Only the use of a nasogastric pH probe during PSG will provide definitive diagnosis, but most sleep laboratories do not routinely perform such testing. Insomnia is a particularly common symptom when GERD and irritable bowel syndrome overlap [39]. Peptic ulcer disease is likely to be identified due to its typical pattern of awakening in the early hours of sleep, with abdominal discomfort or nausea. The untreated condition could certainly produce chronic sleep disruption, but recurrent bouts of ulcer may eventually lead to chronic difficulties with sleep maintenance and persistent early awakening. Pain and discomfort in association with any infectious, inflammatory, allergic, or neoplastic intestinal disorders may cause frequent nocturnal arousal, which may also include prolonged awakenings for bathroom visits, requiring sleep to be reinitiated at a disadvantageous time during the night. Milk allergy [40] and other food allergies [41] have been suggested as a cause of poor sleep in infants. The absence of a specific finding on PSG makes it contingent on the clinician to infer the diagnosis from clinical history, and treatment of the underlying disorder can be combined with short-term or longer-term treatment of secondary insomnia, which is likely to require at least some pharmacotherapy. The symptoms of esophageal reflux may be reduced by smoking cessation, weight loss, avoiding fatty/spicy foods, reducing daily caffeine intake, and treatment with a variety of medications, including antacids, H2-receptor blockers, proton pump inhibitors, and agents that improve gastric motility. Flexible dosing of shorter-acting hypnotic medications may be most appropriate for disorders that have waxing and waning

symptoms (inflammatory bowel disease) that appear at different times of night. Longer-acting hypnotic medications may be required when symptoms are more severe or enduring on a given night. Note that nearly all of the hypnotic medications can aggravate intestinal problems, by dehydrating mucosal linings (tricyclic antidepressants, antihistamines), increasing motility (serotonin reuptake inhibitors), or decreasing motility (benzodiazepines, barbiturates).

Insomnia Associated with Renal Disorders

Poor sleep quality, insomnia, and restless legs syndrome (RLS) are quite common in patients with renal illnesses. Chronic renal disease commonly causes insomnia [42], even early in the development of the disease [43]. Sleep disturbances as defined by a score of higher than 5 on the Pittsburgh Sleep Quality Index (PSQI) occur in 74.4% of patients with renal disease [44].

Using the same scale, 53% of chronic kidney diseases sufferers rate the quality of their sleep as poor [45]. Insomnia occurs in 49% of dialysis patients making it the most common sleep disorder in this group [46]. An earlier study had reported the prevalence of insomnia to be 72% in a similar group of patients [47]. Restless legs syndrome is also quite common in these patients with 21.5% of patients with end-stage renal disease [48] and up to 84% on maintenance dialysis complaining of RLS [47]. Insomnia is worsened by electrolyte fluctuations caused by hemodialysis and the high incidence of PLMS [49] in addition and independent of RLS. Parathyroid hormone may be of particular influence in causing insomnia, and parathyroidectomy has been shown to alleviate insomnia in some patients on hemodialysis [50]. Kidney transplant significantly improves both sleep problems and RLS but does not necessarily resolve them despite eliminating all of the electrolyte shifts and lifestyle confounds of hemodialysis [51]. The prevalence of RLS is significantly lower, however, in kidney transplant patients than in patients on dialysis [52]. One study found that Cognitive behavioral therapy has been shown to be of benefit in a small-cohort study of patients undergoing chronic peritoneal dialysis [53].

Renal disease-associated RLS and resultant sleep disturbances respond to the same treatments that idiopathic RLS does. After correction of any iron deficiency a small dose of benzodiazepine might be beneficial; however, low doses of dopamine agonists are preferred [54]. The use of erythropoietin in patients with renal disease may improve restless legs [55]. If insomnia persists despite elimination of RLS, a small dose of a sedative antidepressant such as trazodone which does not have significant respiratory depressant potential and are primarily metabolized by the liver, may be of help.

Genitourinary System Disturbances and Insomnia

Urological disorders cause sleep disruption by compelling frequent awakening for urination and frequent arousal due to pain. Progressive prostatic hypertrophy compels frequent voiding of small urine volumes, ameliorated somewhat by medications that reduce the size of the prostate. Prostatic carcinoma may cause a similar pattern, and resection of the prostate may produce urinary urgency and incontinence, further exacerbating sleep dysfunction [56].

Pain or discomfort related to interstitial cystitis, prostatitis, bladder infection, or nephrolithiasis may cause awakening or occult nocturnal arousal, resulting in insufficient sleep. Neurogenic bladder dysfunction may produce a hypotonic (overfilled) bladder that requires intermittent catheterization to avoid overflow incontinence, or a hypertonic bladder that produces discomfort and the urge to void with the smallest amount of urine volume. Once the cause of urological dysfunction has been identified and appropriately addressed, the use of hypnotic medications tend to be benign, and the pharmacology of different medications can be chosen for the most practical solution. Tricyclic antidepressant medications tend to cause urinary retention and increase urinary hesitancy, and would not be an ideal choice.

Musculoskeletal Problems and Insomnia

The rheumatoid disorders, and musculoskeletal discomfort in general, are highly associated with chronic sleep disruption. Rheumatoid arthritis [57, 58], ankylosing spondylitis [59], systemic lupus erythematosis [60], vasculitis, polymyalgia rheumatica, and fibromyalgia [61] can produce sleep disruption, which may become a very debilitating aspect of the disease, complicating functional recovery. Insomnia is reported in up to half of the children who have chronic limb pain [62], and daytime pain is reported to be worse following unrefreshing sleep [63]. The pain certainly is a profound trigger of sleep disturbance, as are the effects of glucocorticoid medications [64] commonly used to treat the rheumatoid diseases. The EEG during NREM sleep may include considerable alpha range activity, even in deep sleep (the "alpha–delta" sleep pattern), which was decreased by treatment with sodium oxybate in patients with fibromyalgia [65]. Alpha intrusion is not specific to the rheumatoid disorders; the same pattern may be seen in chronic fatigue syndrome [66], with its cardinal symptoms of idiopathic fatigue, headache, arthralgia, myalgia, and insomnia [67]. Osteoarthritis may become more symptomatic as the morning approaches, after a night of relative immobility, and may result in early awakening. Degenerative change of the spine, scoliosis, and scleroderma may all cause impaired ventilation, leading to frequent arousals and impaired sleep. Cognitive behavioral therapy has been shown to be beneficial for the treatment of insomnia associated with fibromyalgia [68] and in older adults with comorbid conditions including arthritis [69]

Endocrine Causes for Insomnia

Various endocrine disturbances cause insomnia, due to either the activating effects of the hormones or somatic discomfort produced by their imbalances [70]. Insomnia is more prevalent in hyperthyroidism, in association with a globally activated behavioral state, and sleep studies have shown an overall increase in the percentage of deep sleep [71] once difficulties with sleep initiation are overcome. The return to a serological and clinical euthyroid state may not guarantee the resolution of insomnia. Hypothyroidism more commonly causes fatigue and lethargy, and PSG has shown an associated decrease in deep sleep. Parathyroid hormone has been mentioned as a potential cause of insomnia in ESRD hemodialysis patients [50], with insomnia dramatically

improved in some patients following parathyroidectomy. Insomnia symptoms were also improved in symptomatic secondary hyperparathyroidism after parathyroidectomy [72]. However, there was no improvement in subjective reports of insomnia after parathyroidectomy in otherwise asymptomatic primary hyperparathyroidism [73]. Perhaps the improvement in insomnia is not due to the change in parathyroid hormone itself, but because there is improvement in some of the somatic symptoms produced by hyperparathyroidism. Dysfunction causing catecholamine oversecretion will cause sympathetic activation and insomnia, and excessive glucocorticoid levels also cause insomnia [10, 64]. It has been suggested that elevated glucocorticoid levels may alter the production of endogenous GABA-related steroid production [35], causing some of the observed insomnia. Disruption of the hypothalamic–pituitary–adrenal axis has been found in association with chronic insomnia, though it is not clear whether the disruption of hormonal secretion is the cause or effect of insomnia [74, 75]. There is considerable clinical reporting of insomnia during menses [76], with or without associated somatic discomfort, and during menopause [77]. The symptom of insomnia and its management in pregnancy and menopause are discussed in depth in other chapters. Insomnia is reported in up to a third of patients with diabetes mellitus [78]. Treatment of sleep disruption in endocrine disturbance may be complicated by hormonal fluctuations and potential medical complications of therapy, and may require multiple modalities, spanning the pharmacological, behavioral, and alternative therapeutic realms.

Cancer and Insomnia

Cancer may produce insomnia due to pernicious effects on systemic physiology, painful tissue changes, therapeutic efforts, or the anxiety and depression accompanying the diagnosis. Insomnia has been found to occur in over half (53%) of the patients with newly diagnosed lung cancer, and was felt to be a severe symptom in over a quarter [79], especially in association with pain and fatigue [80]. Insomnia occurred in 19% of women with breast cancer, and was of chronic character 95% of the time [81]. There may be premorbid risks that contribute to the development of insomnia after the diagnosis of breast cancer [82, 83] such as depression, anxiety, and of course previous problems with insomnia. Chronic insomnia after treatment for breast cancer may also be influenced by physical discomfort, as would be associated with lymphedema [84]. Insomnia has been examined in a variety of cancer types [85], and has been found to occur in about a third of cases, along with reports of fatigue, leg restlessness, and excessive sleepiness. The fatigue associated with cancer treatment may be partly due to insomnia. [86]. The claudication associated with hematologic disorders such as sickle cell anemia causes severe intermittent sleep disruption [87], made worse by occult sleep-disordered breathing and PLMS. Treatment should take into consideration the anticipated duration of the underlying disease, and any potential medical issues that could complicate pharmacotherapy. Insomnia therapy should be directed to preserve the quality of daytime function, improving sleep with a minimum of residual cognitive dulling, lingering hypnotic effects, or uncomfortable side effects. There may be a role for medications that have antidepressant or anxiolytic characteristics,

especially in the early stages following cancer diagnosis. Chronic treatment may be better achieved by nonpharmacologic interventions [81, 83, 88] such as cognitive therapy, relaxation therapy, biofeedback, and behavioral approaches to improve sleep quality [89–91]. There is some evidence to suggest that cognitive behavioral therapy for the treatment of insomnia in breast cancer may actually enhance immunological function as well [92, 93].

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